PART A

IN THE DISTRICT COURT OF CLEVELAND COUNTY

STATE OF OKLAHOMA, ex rel.,
MIKE HUNTER,
ATTORNEY GENERAL OF OKLAHOMA,
Plaintiff,
vs.
(1) PURDUE PHARMA L.P.;
(2) PURDUE PHARMA, INC.;
(3) THE PURDUE FREDERICK COMPANY,
(4) TEVA PHARMACEUTICALS USA, INC.;
(5) CEPHALON, INC.;
(6) JOHNSON & JOHNSON;
(7) JANSSEN PHARMACEUTICALS, INC,
(8) ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., n/k/a JANSSEN PHARMACEUTICALS;
(9) JANSSEN PHARMACEUTICA, INC., n/k/a JANSSEN PHARMACEUTICALS, INC.;
(10) ALLERGAN, PLC, f/k/a ACTAVIS PLC, f/k/a ACTAVIS, INC., f/k/a WATSON PHARMACEUTICALS, INC.;
(11) WATSON LABORATORIES, INC.;
(12) ACTAVIS LLC; and
(13) ACTAVIS PHARMA, INC., f/k/a WATSON PHARMA, INC.,
Defendants.

For Judge Balkman's Consideration

Case No. CJ-2017-816
Honorable Thad Balkman

William C. Hetherington
Special Discovery Master

DEFENDANTS TEVA PHARMACEUTICALS USA, INC., CEPHALON, INC., WATSON LABORATORIES, INC., ACTAVIS LLC, AND ACTAVIS PHARMA, INC., f/k/a WATSON PHARMA, INC.'S TRIAL BRIEF

IN THE DISTRICT COURT OF CLEVELAND COUNTY

STATE OF OKLAHOMA, ex rel., MIKE HUNTER, ATTORNEY GENERAL OF OKLAHOMA, Plaintiff,	**For Judge Balkman's Consideration**
vs.	
(1) PURDUE PHARMA L.P.;	
(2) PURDUE PHARMA, INC.;	
(3) THE PURDUE FREDERICK COMPANY,	
(4) TEVA PHARMACEUTICALS USA, INC.;	
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(6) JOHNSON & JOHNSON;	
(7) JANSSEN PHARMACEUTICALS, INC,	
(8) ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., n/k/a JANSSEN PHARMACEUTICALS;	**Case No. CJ-2017-816** **Honorable Thad Balkman**
(9) JANSSEN PHARMACEUTICA, INC., n/k/a JANSSEN PHARMACEUTICALS, INC.;	**William C. Hetherington** **Special Discovery Master**
(10) ALLERGAN, PLC, f/k/a ACTAVIS PLC, f/k/a ACTAVIS, INC., f/k/a WATSON PHARMACEUTICALS, INC.;	
(11) WATSON LABORATORIES, INC.;	
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DEFENDANTS TEVA PHARMACEUTICALS USA, INC., CEPHALON, INC., WATSON LABORATORIES, INC., ACTAVIS LLC, AND ACTAVIS PHARMA, INC., f/k/a WATSON PHARMA, INC.'S TRIAL BRIEF

Defendants Watson Laboratories, Inc. ("Watson Labs"), Actavis LLC ("Actavis LLC"), and Actavis Pharma, Inc. ("Actavis Pharma") (collectively the "Actavis Generic Defendants"), and Teva Pharmaceuticals USA, Inc. ("Teva USA") and Cephalon, Inc. ("Cephalon") (collectively the "Teva Defendants") submit the following trial brief outlining the legal and factual issues for trial.

INTRODUCTORY STATEMENT

Of the State's six original claims, only one remains: a single sweeping claim of public nuisance premised upon alleged false marketing of opioid medicines against two groups of pharmaceutical companies for which the State seeks more than $17 billion.[1] The State has no legal or factual bases for its public nuisance claim—which reflects the State's clear intention to exceed the limits of its authority and Oklahoma law. Indeed, after more than a year of discovery, the State cannot prove that the Teva or Actavis Generic Defendants made a single false statement to a single prescriber in Oklahoma—much less misled a single Oklahoma doctor into writing a harmful opioid prescription. The State certainly cannot prove that an "entire community" of Oklahoma patients received harmful and improper opioid prescriptions because of any allegedly false statement by the Teva or Actavis Generic Defendants. There is simply no public nuisance claim.

To avoid these failures, the State attempts to lump all opioid manufacturers together and resorts to rhetoric about the opioid abuse epidemic in Oklahoma. But rhetoric is not evidence. The State has chosen to sue thirteen separate and distinct manufacturers under a public nuisance theory, yet the Court cannot ignore the law or the unique circumstances of the Teva and Actavis Generic Defendants. Consistent with the business model for generic manufacturers, the Actavis Generic Defendants and Teva USA simply do not promote their generic medicines to physicians or the public. And the only two opioid medicines (Actiq and Fentora) marketed by Cephalon are

[1] On December 6, 2017, the Court dismissed the State's Oklahoma Consumer Protection Act claims. Following the close of discovery—during which over two hundred depositions were taken and millions of pages of discovery produced—the State dismissed without prejudice its other claims and has decided to proceed on this one claim. On March 26, 2019, the State settled its claims against the Purdue Defendants for $270 Million. On April 4, 2019, the State of Oklahoma voluntarily withdrew all claims against the remaining Defendants except for its claim of public nuisance and request for abatement. (*see* Ex. A, April 4, 2019 Notice of Voluntary Dismissal of Claims.)

unique: they are short-acting opioids marketed differently from the other Defendants' medicines (which are long-acting opioids); they always have been subject to unique FDA risk-mitigation programs; and they comprise a miniscule share—less than .01%—of all opioid prescriptions in Oklahoma.

Nor does the State account for the many other independent actors that break the State's illusory theory of causation. Once an opioid medicine is sold by a manufacturer, there are many independent actors that determine what happens to that opioid medicine, including the discretionary decision-making of prescribers, distributors, pharmacies, patients, the FDA, DEA, and the State itself. The Teva and Actavis Generic Defendants cannot be held responsible for such independent and intervening conduct, particularly when the State cannot identify a single Oklahoma provider who was supposedly misled by them. By way of example only, the State waited years before it imposed any reimbursement limits on Actiq and Fentora prescriptions for Medicaid patients, and it continues to reimburse for opioid prescriptions for chronic pain today, thereby ensuring that opioids continue to get prescribed and dispensed to Oklahoma patients. The State also failed, among other things, to implement an effective prescription drug monitoring program, pass effective and timely legislation cracking down on pill mills, or otherwise effectively address diversion of opioid medicines. The State cannot sue the Teva and Actavis Generic Defendants for harm that the State helped create.

Based upon the undisputed record, the Teva and Actavis Generic Defendants are entitled to judgment on the State's lone public nuisance claim for at least the following reasons:

- ***First***, the claim against the Actavis Generic Defendants is preempted by federal law and otherwise fails because there is no evidence whatsoever of any marketing done by the Actavis Generic Defendants in Oklahoma, much less any evidence of false marketing;

- ***Second***, the State's public nuisance theory would result in an unprecedented expansion of the law of public nuisance in Oklahoma and has been expressly rejected by other courts;

- ***Third***, the State cannot prove causation as to the Teva and Actavis Defendants;
- ***Fourth***, no "unlawful act" serves as the basis for the State's public nuisance claim;
- ***Fifth***, the alleged false marketing by the Teva and Actavis Generic Defendants did not impact the Oklahoma community as a whole, much less at the same time;
- ***Sixth***, the State's public nuisance claim is barred by the two-year statute of limitations;
- ***Seventh***, the State's abatement remedy is an improper form of relief, not tailored to abating the nuisance (allegedly false marketing of opioid medicines), and violates the Free Public Services Rule;
- ***Eighth***, joint and several liability does not apply as a matter of law; and
- ***Ninth***, the State's claim is barred by the doctrines of laches and equitable estoppel.

For these reasons and others, the State cannot prevail at trial on its claim of public nuisance against the Teva and Actavis Generic Defendants.

ARGUMENTS AND AUTHORITIES

I. The State Must But Cannot Prove Its Claims By Clear And Convincing Evidence.

The State must prove its case by ***clear and convincing*** evidence because it seeks to abate the alleged nuisance. *See Meinders v. Johnson*, 2006 OK CIV APP 35, ¶13, 17, 134 P.3d 858, 862, 864; *see also McPherson v. First Presbyterian Church of Woodward,* 1926 OK 214, 248 P. 561. Abatement is an equitable remedy. *See, e.g., State v. Twin C Convenience Store*, 218 P.3d 529, 532 (Okla. Civ. App. Ct. 2009). Because the relief sought is equitable in nature, rather than legal, the State bears the burden of proving its case by clear and convincing evidence. *Burlington N. & Santa Fe Ry. Co. v. Grant,* 505 F.3d 1013, 1022–23 (10th Cir. 2007) (discussing abatement and establishing that the burden of proof under Oklahoma law for injunctive relief is clear and convincing evidence). It cannot do so.

II. Each Manufacturer of Opioids Is Different And The State Cannot Avoid These Differences By Lumping Them All Together.

The State has made clear that it seeks to prove its case by lumping together all Defendants, including the various companies that compromise the Teva Defendants, the Actavis Generic Defendants, the Janssen Defendants, and the now settled Purdue Defendants. In so doing, the State seeks to elide key differences, including the different products they manufacture, the unique indications for which they were and are prescribed, when they manufactured them, and if they marketed or promoted them. This approach is flawed as a matter of law—and cannot remedy the absence of any evidence against the Teva and Actavis Generic Defendants. *See, e.g., N.L.R.B. v. Greater Kansas City Roofing*, 2 F.3d 1047 (10th Cir. 1993); *Buckner v. Dillard*, 1939 OK 144, 184 Okla. 586, 89 P.2d 326, 329.

Defendants manufacture and sell many different, often competing, opioid products with different release dates, different approved clinical indications, different product labels, and different promotional strategies, if any. For instance, the State has consistently and repeatedly traced all harm caused by the opioid epidemic to the approval, launch, and marketing of OxyContin by the Purdue Defendants in 1996. *See, e.g.*, Ex. B, 8/30/18 Hearing Transcript, at 57:17–58:1 (Beckworth, B.) ("You can trace it to a very specific point in time, and that is when OxyContin was brought to market and promoted in an aggressive, concentrated, and targeted way to consumers and doctors, practitioners, prescribers, and pharmacists across this country. That's what happened."). This has nothing to do with the Teva and Actavis Generic Defendants.

Indeed, the Teva and Actavis Generic Defendants in particular are uniquely situated. Unlike any other company in this lawsuit, Watson, Actavis Pharma, and Actavis LLC have always manufactured generic medicines. Consistent with the business model for generic manufacturers,

the Actavis Generic Defendants have not promoted their generic medicines—in Oklahoma or anywhere else. Similarly, before 2011, Teva USA sold only generic opioid medicines and did not market them; it only became affiliated with Cephalon in 2011.

Likewise, Cephalon is uniquely situated because it only ever manufactured and promoted two branded schedule II opioid medicines—Actiq and Fentora. Cephalon launched Actiq in 2001, five years after the State contends that the Purdue Defendants created the opioid epidemic, and then launched Fentora in 2006. Unlike the long-acting opioids sold and manufactured by other Defendants, Actiq and Fentora are immediate-release—or "short-acting"—opioids. They are indicated and approved by the FDA for the management of ***breakthrough cancer pain*** in patients who are tolerant to opioid therapy for their underlying persistent cancer pain. They do not treat long-term pain.

Because of their potency, Actiq and Fentora always have been subject to FDA-mandated risk mitigation programs to ensure that doctors are aware of the risks of these medicines. From the time of their respective launches in 2001 (Actiq) and 2006 (Fentora), they were subject to risk management plans ("RMPs"). The Actiq and Fentora RMPs were designed to address and prevent potential risk situations, including accidental ingestion, improper patient selection, diversion, and abuse.

Moreover, since March 2012, prescribers who wished to prescribe Actiq or Fentora (or their generic equivalents) were required to comply with the stringent requirements of a special Risk Evaluation and Mitigation Strategy ("REMS") applicable to this class of transmucosal immediate-release fentanyl ("TIRF") prescription medicines ("TIRF REMS"). (TIRF REMS, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/rems/TIRF_SS_2015-12-21_REMS_FULL.pdf, attached hereto as Exhibit C.) The TIRF REMS Program imposes additional, unique, and rigorous

requirements on doctors, patients, and pharmacies to ensure that patients receive only medically appropriate prescriptions of Actiq and Fentora. *See* 21 U.S.C. § 355-1 (governing REMS programs); TIRF REMS, Ex. C.

For example, the TIRF REMS Program requires each prescriber of Actiq and Fentora to review educational materials, including the full prescribing information, and successfully complete a knowledge assessment, before being eligible to prescribe these medicines. (*Id.* ¶ II(B)(1)(b)(i); *see also id.* at 51–53 ("Prescriber Enrollment Form;" certifying prescriber has reviewed "Full Prescribing Information" and understands "***responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy***" (emphases added).) In addition, both patient and physician must sign a TIRF REMS Access Patient-Prescriber Agreement Form ("Patient Form") ***before*** the patient's first prescription. (*Id.* ¶ II(B)(1)(b)(ii).) The Patient Form requires both patient and physician to agree that they each ***understand the risks, consequences, and approved uses*** of TIRF medicines." (*Id.*)

Given their unique indications and the stringent TIRF REMS Program, it is not surprising that Actiq and Fentora make up a miniscule proportion of the opioid medicines sold in Oklahoma. In fact, between January 1, 2007 and June 21, 2016, the Oklahoma Health Care Authority ("OCHA") reimbursed a mere 245 prescriptions of Actiq and Fentora, for which the State paid less than $650,000--that is less than .01% of all opioid prescriptions in Oklahoma. (Pet., Ex. D, ¶ 37.)

Even more telling, the State's expert disclosures have not identified ***any*** of the 245 Actiq or Fentora prescriptions (out of the 9 million) reimbursed by OHCA that were medically unnecessary. ***Zero.*** Nor can the State do so, because, the State limited reimbursement for Actiq and Fentora to only cancer-related diagnoses for at least the past decade. (*See* Oklahoma Healthcare Authority,

Prior Authorization Guide, 2009, https://okhca.org/providers.aspx?id=11342#34, attached hereto as Exhibit E.)

III. The Public Nuisance Claim Against The Actavis Generic Defendants Fails Because There Is No Evidence of Marketing Done By the Actavis Generic Defendants In Oklahoma And Any Other Theory Is Preempted.

The Actavis Generic Defendants manufacture and sell certain generic opioid medicines. They have never promoted the efficacy or safety of their generic products—and do not use third parties to do so either. This business model differs from how brand manufacturers market and promote their medicines, and is primarily the result of drug substitution laws, where, to save costs, the pharmacist substitutes a generic product for the more expensive branded medicine once a prescription is written. *See, e.g.*, Okla. Administrative Code § 535:10–3-1.1(2) (drug substitution law). Because a prescriber has ***no control*** over which generic manufacturer's product is substituted at the pharmacy, generic products are not marketed to prescribers:

> [B]ecause the generic [firm] promoting the product would have no way to ensure that its generic product, rather than an AB-rated generic made by one of its competitors, would be substituted for the brand by pharmacists, a substantial investment in marketing a generic product to physicians would not make sense as a practical matter.

See New York v. Actavis, PLC, No. 14 CIV 7473, 2014 WL 7015198, at *27 (S.D.N.Y. Dec. 11, 2014). Of course, the State cannot succeed on its public nuisance claim premised upon false marketing against companies that do not market their medicines.

To the extent that the State's public nuisance claim is premised upon any other theory, such as an omission theory, it is preempted by federal law. *See, e.g.*, *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011); *Mutual Pharmaceutical Co., v. Bartlett*, 570 U.S. 472 (2013). The Federal Food Drug & Cosmetic Act ("FDCA") and its accompanying regulations impose a duty of "sameness" on generic manufacturers: it prohibits a generic drug manufacturer from issuing additional warnings beyond those in the labels for their brand counterparts. *See* 21 U.S.C. § 355(j)(2)(A). Under this

"sameness" requirement, generic manufacturers are not permitted to communicate ***any warnings*** beyond a generic label if brand-name manufacturers have not already sent such a communication, because doing so "would inaccurately imply a therapeutic difference between the brand and generic drugs and thus could be impermissibly 'misleading.'" *Mensing,* 564 U.S. at 615 (claims that generic drug manufacturers failed to send "Dear Doctor" Letters to healthcare professionals regarding generic medicine's risks were preempted because they would violate federal law); *Morris v. PLIVA, Inc.*, 713 F.3d 774, 777 (5th Cir. 2013) (applying rule); *Guarino v. Wyeth, LLC*, 719 F.3d 1245, 1249 (11th Cir. 2013) (applying rule).

The State contends that Teva USA and the Actavis Generic Defendants can be held liable merely because they sold their generic medicines and benefited from the marketing of other brand manufacturers. Not so. The State cannot avoid preemption by arguing that the Generic Manufacturers should have stopped selling FDA-approved drugs altogether because of insufficient warnings about opioids. *See Morris*, 713 F.3d at 778 ("Any state law-based holding that the generic manufacturers should have acted differently with respect to warnings or should have ceased manufacturing these products because of insufficient warnings not only violates the duty of sameness but conflicts with FDA's exclusive authority to approve drugs and drug labels."). The State's entire theory of liability as to generic medicines fails as a matter of law.

IV. The State's Theory of Liability Is Not Grounded In The Law And Would Result In An Unprecedented Expansion Of The Law Of Public Nuisance In Oklahoma.

The law of nuisance in Oklahoma has been historically and fundamentally concerned with the misuse of, or interference with, land and real property. *See, e.g., Laubenstein v. Bode Tower, L.L.C.*, 392 P.3d 706, 709 (Okla. 2016) ("We have said that a nuisance arises from an unreasonable, unwarranted, or unlawful use *of property*." (emphasis added)). And no case in Oklahoma

embraces the State's view that public nuisance encompasses harm caused by the allegedly false marketing and sale of FDA-approved products.

A survey of public nuisance cases in Oklahoma makes clear that public nuisance law in Oklahoma is generally limited to addressing interference with the use and enjoyment of real property. For example, many Oklahoma public nuisance decisions concern the pollution of land or water. *See, e.g., N.C. Corff P'ship, Ltd. v. OXY USA, Inc.*, 929 P.2d 288, 293–96 (Okla. Civ. App. 1996) (groundwater pollution from oil and gas wells); *Meinders v. Johnson*, 134 P.3d 858, 860, 867–68 (Okla. Civ. App. 2005) (sub-surface pollution from mineral exploration). Others concern the misuse of private property for other sorts of obnoxious, dangerous, or immoral purposes. *See, e.g., State ex rel. Fallis v. Mike Kelly Constr. Co.*, 638 P.2d 455, 456 (Okla. 1981) (operation of "open saloon"); *Boudinot v. State ex rel. Cannon*, 340 P.2d 268, 269 (Okla. 1959) ("noise and odor arising" from defendant's "keeping a large number of cats on her residential property"). And others concern the misuse of public lands and roads. *See, e.g., State ex rel. Burk v. Oklahoma City*, 522 P.2d 612, 615 (Okla. 1973) (construction of building on public street).

The State's claim has nothing to do with the misuse of or interference with property. Instead, the State alleges that it has suffered a variety of different harms, including derivative expenses (*e.g.*, healthcare costs, social services, criminal justice) arising from injuries to consumers of FDA-approved medicines sold and marketing by the Defendants in this case. (*See* Pet. ¶ 119.) In simple terms, the State's claim sounds entirely in products liability, not public nuisance. Nuisance and product liability are separate and distinct bodies of law, and courts across the nation have held that they must remain that way.[2]

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[2] In 2008, the Rhode Island Supreme Court refused to hold lead paint manufacturers liable under a public nuisance theory. "The law of public nuisance," the court recognized, "never before has been applied to products, however harmful." *State v. Lead Indus., Ass'n, Inc.*, 951 A.2d 428, 456

Indeed, only two weeks ago, a North Dakota court dismissed a nearly identical public nuisance claim—brought under a nearly identical public nuisance statute—against opioid manufacturers on the basis that "[n]o North Dakota court has extended the public nuisance statutes to cases involving the sale of goods." Ex. J, *State of North Dakota v. Purdue Pharma,* Case No. 08-2018-cv-01300 (Order 5/10/19) (dismissing similar claims, including public nuisance claim, because manufacturer of opioids has no control over the product once it enters the market).

Consistent with this legal principle, other courts presiding over nearly identical public nuisance claims have dismissed those claims because "[t]here is a clear national trend to limit public nuisance to land use" rather than product-based claims. *State ex rel. Jennings v. Purdue Pharma L.P.*, No. CVN18C01223MMJCCLD, 2019 WL 446382, at *12 (Del. Super. Ct. Feb. 4, 2019). Indeed, state and federal courts across the country—in cases involving a wide array of products— have agreed that public nuisance liability should not be imposed as a substitute for products liability. *See, e.g.*, *Camden Cty. Bd. of Chosen Freeholders v. Beretta, U.S.A. Corp.*, 273 F.3d 536, 540 (3d Cir. 2001) (firearms) ("[T]he courts have enforced the boundary between the well-developed body of product liability law and public nuisance law."); *Ashley Cty. v. Pfizer, Inc.*, 552 F.3d 659, 671–72 (8th Cir. 2009) (cold medicine) (same); *City of Perry v. Procter & Gamble Co.*, 188 F. Supp. 3d 276, 291 (S.D.N.Y. 2016) (flushable wipes) ("The parties do not cite, and the Court is not aware of, any cases applying Iowa law that recognize a nuisance claim arising out of the sale or use of a product as opposed to the use of property."); *Detroit Bd. of Educ.*

(R.I. 2008). Whereas "[p]ublic nuisance focuses on the abatement of annoying or bothersome activities[,] [p]roducts liability law, on the other hand, has its own well-defined structure, which is designed specifically to hold manufacturers liable for harmful products that the manufacturers have caused to enter the stream of commerce." *Id.* The court continued: "Undoubtedly, public nuisance and products liability are two distinct causes of action, each with rational boundaries that are not intended to overlap. *Id.*; *see also id.* at 457.

v. Celotex Corp., 493 N.W.2d 513, 521 (Mich. Ct. App. 1992) (asbestos) ("The law of nuisance is fraught with conditional rules and exceptions that turn on the facts of individual cases, and the cases almost universally concern the use or condition of property, not products.").

Even the drafters of the most recent Restatement—the Third Restatement of Torts—have recognized and approved this trend of denying products liability claims cloaked as public nuisance claims, observing that "the common law of public nuisance is an inapt vehicle for addressing the conduct at issue" in cases of dangerous products. Restatement (Third) of Torts: Liability for Economic Harm § 8 TD No. 2 cmt. g (2014). As a matter of law, this Court should do the same.

Because the no Oklahoma court has ever recognized the type of nuisance claim brought here and because doing so would improperly expand the scope and purpose of nuisance law, the State simply cannot succeed on its claim at trial.

V. The State Cannot Prove Causation.

A. The Claim Fails As A Matter Of Law Because The Causal Chain Is Too Attenuated.

In order for the State to prevail on its public nuisance claim, it must prove by clear and convincing evidence that the Teva and Actavis Generic Defendants' supposedly false statements about opioids caused medical professionals to write medically unnecessary opioid prescriptions, which, in turn, caused various harm to an "entire community" that the State must now abate. (Ex. D, Pet. ¶¶ 116–120.) But as a matter of law, the Teva and Actavis Generic Defendants' conduct—none of which was unlawful—is simply too attenuated from those downstream harms to be held responsible. Even if the Court were to accept the State's legally unsupportable theory of Oklahoma's public nuisance law (which it should not), there is no legal or factual basis for finding that the Teva and Actavis Generic Defendants *proximately caused* the public nuisance.

At every turn, there are independent actors that break the chain of causation against the Teva and Actavis Generic Defendants. At a minimum, for each opioid-related harm that the State seeks to abate, the chain of causation would include at least the following links:[3]

- ***Link One***: The Teva or Actavis Generic Defendants manufacture the opioid medicine;
- ***Link Two***: The FDA approves the sale of the medicines and their labeling;
- ***Link Three***: The DEA sets quota limits to ensure that there is no "oversupply" of opioid medicines in the market;
- ***Link Four***: An Oklahoma prescriber receives marketing material for branded opioid medicines attributable to the Actavis and Teva Defendants and that marketing material is false or misleading in violation of an Oklahoma law;
- ***Link Five***: Instead of exercising her own independent medical judgment, the Oklahoma prescriber writes a prescription for an opioid medicine to an Oklahoman because of an allegedly false statement made by the Actavis or Teva Defendants and without knowledge or an understanding of the risks of the medication as a learned intermediary, despite prominent and extensive labeling information provided on the medication—and, after 2012, despite the stringent TIRF REMS requirements;[4]
- ***Link Six***: Reimbursement policies by managed care organizations, like insurance companies, do not cause the Oklahoma prescriber to write the opioid prescription;

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[3] This causal chain is not exhaustive and merely provides the Court with some of the elements and various actors involved in the manufacture, sale, prescription, distribution, and diversion of opioid medicines.

[4] Since the beginning of 2012, Actiq and Fentora have been subject to a special Risk Evaluation and Mitigation Strategy ("REMS") applicable to the class of transmucosal immediate-release fentanyl ("TIRF") prescription medicines. *See* 21 U.S.C. § 355-1 (governing REMS programs); TIRF REMS, Ex. C, available at http://www.accessdata.fda.gov/drugsatfda_docs/rems/TIRF_SS_2015-12-21_REMS_FULL.pdf. The TIRF REMS Program requires (1) an FDA-approved medication guide to be provided to patients before the medication is dispensed in an outpatient setting; (2) each prescriber of Actiq or Fentora to review educational materials, including the full prescribing information, and to successfully complete a knowledge assessment, ***before being eligible to prescribe*** Actiq or Fentora; and (3) both patient and prescriber must sign a TIRF REMS Access Patient-Prescriber Agreement Form before the patient's first prescription acknowledging that they understand the risks, consequences, and approved uses of TIRF medicines. (*Id.* ¶¶ II(A), II(B)(1)(b)(i), II(B)(1)(b)(ii).)

- ***Link Seven***: The patient chooses to fill the medically inappropriate prescription without any knowledge about the risks of the medication;

- ***Link Eight:*** A distributor sells opioids to the pharmacy, without flagging the sale as suspicious;

- ***Link Nine***: The pharmacist first decides whether to substitute a generic medicine for a branded medicine and then dispenses the medically unnecessary opioid prescription, without informing the patient about the risks or deeming the prescription to be medically unnecessary;

- ***Link Ten***: The Oklahoma Health Care Authority does not reimburse for the prescription, thereby deeming the prescription to be medically necessary (and appropriate)--which it did for over 9 million opioid prescriptions after 1996)[5];

- ***Link Eleven***: The patient, or someone who illegally obtained the opioid from the patient, misuses, abuses, and/or becomes addicted to opioids due to the allegedly fraudulently-induced prescription, as opposed to other factors or other medically appropriate prescriptions; and

- ***Link Twelve***: The patient or someone else who illegally diverted the opioid medicine suffers physical or other harm as a result of the medically unnecessary prescription, as opposed to numerous other factors or circumstances.

These multiple layers of discretionary and fact-intensive decision-making would require an analysis of each prescription, why it was prescribed, why it was dispensed, how it was taken, how it was used, whether it was diverted, and whether it caused any harm. These intervening links render too remote the nexus between any marketing and any downstream harm that forms the basis for the State's public nuisance claim. *Woodward v. Kinchen*, 1968 OK 152, 446 P.2d 375, 377–78 ("[L]iability cannot be predicated on a prior and remote cause which merely furnishes the condition for an injury resulting from an intervening, unrelated and efficient cause."); *Lexmark*

[5] If the Oklahoma Health Care Authority *did* reimburse for a particular prescription, then any harm that resulted from that prescription could not have been caused by the Teva or Actavis Generic Defendants because the State only reimbursed for prescriptions it independently deemed "medically necessary."

Int'l, Inc. v. Static Control Components, Inc., 572 U.S. 118, 132 (2014) (holding that common-law proximate causation principles are incorporated into statutes).

Given the many independent links in this chain of causation, courts have repeatedly dismissed similar claims based upon false marketing because the chain of causation is too indirect and too speculative, particularly where the independent decision-making of medical professionals is a link in the chain. *See. e.g., Ironworkers Local Union No. 68 v. AstraZeneca Pharm. LP*, 585 F. Supp. 2d 1339, 1344 (M.D. Fla. 2008) (applying rule to dismiss similar claims because whether "Plaintiffs' injuries were caused by Defendants' misconduct would require an inquiry into the specifics of each doctor-patient relationship implicated by the lawsuit"); *see, e.g., Sidney Hillman Health Ctr. of Rochester v. Abbott Labs.*, 873 F.3d 574, 578 (7th Cir. 2017) (rejecting claims against pharmaceutical manufacturers because "there are so many layers, and so many independent decisions, between promotion and payment that the causal chain is too long to satisfy" proximate causation); *United Food & Commercial Workers Cent. Pa. & Reg'l Health & Welfare Fund v. Amgen, Inc.*, 400 F. App'x 255, 257 (9th Cir. 2010) (affirming dismissal where, *inter alia*, no "cognizable theory of proximate causation that link[ed] [manufacturer's] alleged misconduct to Appellant's alleged injury" due to intervening links, including "doctors' decisions to prescribe [the medication]"); *In re Yasmin & Yaz (Drospirenone) Mktg., Sales Practices & Prods. Liab. Litig.*, 2010 WL 3119499, at *7–9 (S.D. Ill. 2010) (claims dismissed where court would "have to delve into the specifics of each physician patient relationship to determine what damages were caused by [the] alleged fraudulent conduct, as opposed to what damages were caused by the physician's independent medical judgment").

1. Example 1: Independent Decision-Making Of Prescribers.

Take just one example of why the chain of causation is simply too attenuated: the independent decision-making of prescribers. Under Oklahoma law, a physician acts as a "learned intermediary" because he or she exercises independent judgment in deciding whether to issue a prescription. *Tortorelli v. Mercy Health Ctr., Inc.*, 2010 OK CIV APP 105, ¶ 26, 242 P.3d 549, 560 ("[a] major underlying assumption of the learned intermediary doctrine is that a product has properties rendering it dangerous so as to require a doctor's prescription or order for its use"). As a matter of law, that physician must be aware of the risks in the labels of the medicines he or she prescribes, and, as discovery has demonstrated, Oklahoma physicians have long been aware of such risks. (Ex. F, J. Halford Dep., Feb. 22, 2019, 26:10–27:4; Ex. G, G. Schick Dep., Mar. 1, 2019, 14:1–24; Ex. H, S. Crawford Dep., Feb. 13, 2019, 38:7–23.)

In addition, many Oklahoma prescribers never received any marketing from the Teva and Actavis Generic Defendants, and, thus, could not have been misled by anything they said. (*See, e.g.* (Ex. F, J. Halford Dep., Feb. 22, 2019, 85:14–23; Ex. H, S. Crawford Dep., Feb. 13, 2019, 253: 20–253:24; *Id.* 255:8–255:12; *Id.* 257:6–257:13.) And still other Oklahoma prescribers have made clear that even if they received marketing materials, they were not influenced by that marketing—much less any false marketing. (Ex. G, J. Halford Dep., Feb. 22, 2019, 93:16–22; *Id.* 85:19–87:4; *Id.* 175:1–12; *Id.* 243:8–244:4; *Id.* 78:17–20; Ex. H, S. Crawford Dep., Feb. 13, 2019, 178:17–23; *id.* 264:9–23.) The State cannot show that a single Oklahoma prescriber abandoned her independent medical judgment and wrote an opioid prescription because of any false statement or omission by the Teva or Actavis Generic Defendants, as opposed to the many other factors that influence such decision-making. This layer alone in the causation chain defeats the State's claim.

2. Example 2: Criminal Conduct Of Prescribers, Pill Mills, And Others.

Other examples that defeat the chain of causation abound. The State has prosecuted and convicted Oklahoma prescribers for writing illegal prescriptions of opioids in exchange for money, drugs, or sex. The State also has prosecuted individuals for operating illegal pill mills and illegally selling prescription medicines. As a matter of law, the Teva and Actavis Generic Defendants cannot be held responsible for any harm caused by that independent illegal conduct. *See, e.g., Prince v. B.F. Ascher Co.*, 2004 OK CIV APP 39, ¶ 20, 90 P.3d 1020, 1028 (there is no duty to "anticipate and prevent the intentional or criminal acts of a third party"); *Butler By & Through Butler v. Oklahoma City Pub. Sch. Sys.*, 1994 OK CIV APP 22, 871 P.2d 444, 446 (proximate cause exists only if conduct causes injury "in a natural and continuous sequence, unbroken by any independent cause").

Recognizing the complete lack of Oklahoma case law to support its expansive theory of public nuisance, the State has urged the Court to adopt North Dakota's definition of a public nuisance—which the State characterizes as negating any sort of causal requirement. (Ex. I, 4/11/19 Hr'g Tr. 14:17–16:9, Beckworth, B.) But North Dakota law rejects the State's very interpretation. Indeed, a North Dakota court recently held ***the opposite*** in dismissing a nearly identical lawsuit brought by the North Dakota Attorney General. In *State of North Dakota v. Purdue Pharma, et al.*, the court held:

> The State is clearly seeking to extend the application of the nuisance statute to a situation where one party has sold to another a product that ***later*** is alleged to constitute a nuisance. The reality is that Purdue has no control over its product after it is sold to distributors, then to pharmacies, and then to consumers, i.e. after it enters the market. Purdue cannot control how doctors prescribe its products and it certainly cannot control how individual patients use and respond to its products, regardless of any warning or instruction Purdue may give. No North Dakota court has extended the public nuisance statutes to cases involving the sale of goods.

Ex. J, *North Dakota v. Purdue Pharma,* Case No. 08-2018-cv-01300 (Order 5/10/19) (emphasis added, citations omitted).

The same logic applies here, too. The Teva and Actavis Generic Defendants do not "control" how doctors prescribe their products, how patients use their products, or how the countless other actors distribute, dispense, regulate, consume, or divert opioid medicines. As discovery has confirmed, the chain of causation is simply too attenuated for the Teva or Actavis Generic Defendants to be held liable and a judgment should be entered in their favor.

B. Even If The Causal Chain Was Not Too Attenuated, The State Offers No Evidence Of Causation As To Any Of The Teva Or Actavis Generic Defendants.

Beyond the legal flaws in the State's theory of the case, the State lacks any evidence to establish but-for causation. Critically, there is no evidence whatsoever that any false statements attributable to the Teva and Actavis Generic Defendants caused any Oklahoma prescriber to write an inappropriate opioid prescription that ultimately led to opioid abuse, addiction, or death. And there is certainly no evidence that any such alleged false marketing harmed an "entire community," 50 Okla. Stat. § 2, as opposed to the many other factors that have contributed to opioid-related problems in Oklahoma.

As an initial matter, neither the State nor its experts have provided any actual model to attempt to show causation as to the Teva or Actavis Generic Defendants. They have not done a survey of Oklahoma providers. They have not interviewed any Oklahoma doctors. They have not done any regression modeling to show whether any Oklahoma prescriber received, much less was influenced by, any false marketing by the Teva or Actavis Generic Defendants. Indeed, the Actavis Generic Defendants and Teva USA do not even market their generic medicines to prescribers. As

the evidence at trial will show, the State cannot identify a single prescriber who was misled by any marketing done by the Teva or Actavis Generic Defendants.

There is a good reason for this failure: Oklahoma prescribers made independent medical decisions to prescribe opioid medicines based on numerous factors, including their education, their experience and training, the circumstances of the patient, and whether the opioid medicine is covered by insurance. As federal law makes clear, because there is no evidence of causation, the State cannot prevail on its claim at trial.

In fact, Oklahoma doctors could ***not*** have been misled by any marketing attributable to the Teva or Actavis Generic Defendants into writing harmful prescriptions of Actiq, Fentora, or any other opioid medicine. The labels of opioid medicines accurately disclosed their risks, such that prescribers and patients knew or should have known of the risks associated with opioid use. Moreover, since March 2012, prescribers who wished to prescribe Actiq or Fentora (or their generic equivalents) were required to comply with the stringent requirements of a unique FDA-mandated Risk Evaluation and Mitigation Strategy ("REMS")—specifically tailored to the narrow class of transmucosal immediate release fentanyl ("TIRF") opioids that includes Actiq and Fentora—before writing a prescription of these medicines. 21 U.S.C. § 355-1 (governing REMS programs); Ex. C, TIRF REMS Program. This includes passing a knowledge assessment, reviewing the FDA-approved medication guides for Actiq and Fentora with the patient, and signing an agreement—with the patient—that the prescriber understands and has counseled her patient about the risks and approved uses of Actiq and Fentora, including the risks of abuse, addiction, and even death. *Id.* Clearly, no prescriber who had to certify in writing that he or she was aware of the risks of Actiq and Fentora was misled into writing such a prescription.

Unable to provide any evidence to support its causation theory, the State intends to rely

upon documents pertaining to other manufacturers and statistics that opioid prescriptions generally increased after 1996 when Purdue launched OxyContin. This evidence has nothing to do with the Teva or Actavis Generic Defendants. For instance, the State intends to rely upon a report by the President's Commission on Combating Drug Addiction and the Opioid Crisis (the "Report") to try to meet its causation burden. But this Report says nothing about Oklahoma. It says nothing about any false marketing in Oklahoma. And it refers to specific marketing efforts by ***Purdue***—with which the State settled. The Report does not even mention the Teva or Actavis Generic Defendants. At most, the Report shows that while others may be responsible, the Teva and Actavis Generic Defendants are ***not responsible*** for the opioid crisis in Oklahoma.

At best, the State offers an argument about correlation—that more money spent on marketing leads to more sales of products. But this says nothing about any ***false*** marketing (i.e., the alleged nuisance), and, of course, "correlation does not equal causation." *Western Ry. Co. v. Ayers*, 538 U.S. 135, 173 (2003); *see also Norfolk & W. Ry. Co. v. Ayers*, 538 U.S. 135, 173 (2003) ("Correlation is not causation . . . This correlation the Court relies upon does not establish a direct link between asbestosis and asbestos-related cancer"). The State's causation theory boils down to pure speculation—which is wholly insufficient to impose billions of dollars of liability on the Teva or Actavis Generic Defendants.

Put simply, despite having dozens of experts and years to put together its case, the State lacks any evidence of causation as to the Teva and Actavis Generic Defendants: no survey of doctors, no regression model, and no testimony from any Oklahoma doctor that he or she was misled into writing any harmful opioid prescription because of a statement attributable to the Actavis or Teva Defendants. Of course, the reason is clear: there is simply no such evidence.

VI. The State Lacks Any Evidence Of An "Unlawful Act" To Support Its Public Nuisance Claim.

The public nuisance statute is clear: "For an act or omission to be a nuisance in Oklahoma, it ***must be unlawful***." *Nuncio v. Rock Knoll Townhome Vill., Inc.*, 2016 OK CIV APP 83, ¶ 8, 389 P.3d 370, 374 (emphasis added); *see* 50 Stat. Ann. § 1 (limiting nuisance to actions or omissions done "unlawfully"). And "in the case of a public nuisance [the nuisance] never becomes in itself lawful. It is not unlawful as to the whole public, and lawful as to its constituents, or a part of its constituents. It is absolutely and wholly unlawful." *Revard v. Hunt*, 1911 OK 425, 29 Okla. 835, 119 P. 589, 593; *see also State ex rel. Draper v. Lynch,* 137 P.2d 949, 952 (Okla. 1943) (violation of statute prohibiting lotteries constitutes an "unlawful act" for purposes of bringing a nuisance claim); *James v. State*, 4 Okla. Crim. 587, 112 P. 944 (1911) (violation of gambling statute constitutes an "unlawful act"); *State ex rel. Field v. Hess*, 1975 OK 123 (violation of statute prohibiting selling or trafficking obscene works is an unlawful act such that "[t]he statutory definition of 'nuisance' is satisfied.").

Here, the State argues that the unlawful act was false marketing in Oklahoma. But the State cannot meet its clear and convincing burden to prove any unlawful act committed in Oklahoma by the Teva and Actavis Generic that annoyed, injured, or endangered the health or safety of others.

A. The Teva and Actavis Generic Defendants Did Not Engage In Any Unlawful Conduct In Oklahoma.

The Actavis Generic Defendants and Teva USA did not promote their generic medicines. Thus, there is no unlawful act that they engaged in anywhere, let alone in Oklahoma.

And Cephalon marketed only two branded opioid medicines: Actiq and Fentora. These medicines, however, are unique short-acting opioids and comprise a miniscule share of the

Oklahoma market (*i.e.*, less than .1%). In addition, the FDA approved all Actiq-related marketing materials, and the Fentora materials were submitted to the FDA's Division of Drug, Marketing, Advertising, and Communications ("DDMAC"). In fact, all marketing materials were reviewed and approved by an internal Cephalon committee before they were used by sales representatives. The State's assertion of a fraudulent marketing campaign to dupe physicians into writing inappropriate prescriptions of Actiq and Fentora rings hollow.

To try to show an unlawful act, the State intends to cherry-pick a few notes (referred to as "call notes") of visits involving Cephalon sales representatives with Oklahoma prescribers from more than a decade ago. But the State has not interviewed any of these providers. The State is not going to call any of these physicians as witnesses. The State offers no context for any of those discussions. And the State has no evidence showing that any of these physicians were misled into writing an opioid prescription that they would not otherwise have written because of some false statement or omission by Cephalon.

At most, these call notes show a few instances where sales representatives might have discussed the use of Actiq or Fentora with prescribers outside of the cancer context. But it is black-letter law that such off-label discussions are not inherently "false or misleading." *United States v. Caronia*, 703 F.3d 149, 165 (2d Cir. 2012); *In re Actimmune Mktg. Litig.*, 614 F. Supp. 2d 1037, 1051 n.6 (N.D. Cal. 2009) ("off-label marketing of an approved drug is itself not inherently fraudulent").[6] The First Amendment also protects "speech promoting the lawful, off-label use of

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[6] In addition, "[c]ourts and the FDA have recognized the propriety and potential public value of unapproved or off-label drug use." *United States v. Caronia*, 703 F.3d 149, 153 (2d Cir. 2012); *see also Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 n.5 (2001) (off-label prescribing "often is essential to giving patients optimal medical care"); Use of Approved Drugs for Unlabeled Indications, FDA Drug Bulletin, Vol. 12, No. 1, at 4-5 (Apr. 1982) ("accepted medical practice often includes drug use that is not reflected in approved drug labeling") (quoted in *Weaver v. Reagen*, 886 F.2d 194, 198 (8th Cir. 1989)).

an FDA-approved drug." *Caronia*, 703 F.3d at 169; *see also Sorrell v. IMS Health Inc.*, 564 U.S. 552, 557 (2011) ("[s]peech in aid of pharmaceutical marketing, however, is a form of expression protected by the Free Speech Clause of the First Amendment"). For these very reasons, numerous courts have rejected claims against the Teva Defendants based upon the off-label promotion of opioid medicines. *See Travelers Indem. Co. v. Cephalon, Inc.*, 32 F. Supp. 3d 538, 552 (E.D. Pa. 2014), *aff'd*, 620 F. App'x 82 (3d Cir. 2015); *Ind./Ky./Ohio Reg'l Council of Carpenters Welfare Fund v. Cephalon, Inc.*, No. 13-7167, 2014 WL 2115498, at *5–7 (E.D. Pa. May 21, 2014).

Moreover, Cephalon has always had policies in place to prevent the false or misleading marketing of its opioids medicines. Cephalon's 2004 Sales Policy Handbook (the "2004 Handbook"), for instance, referenced 11 specific policies that were in place at the time and that sales representatives had to follow, including the following: (1) Policy on Advertising and Promotional Materials and Activities, (2) Policy on Identifying Called on Universe of Physicians in Connection with Promotional Activities, (3) Policy Regarding Medical Information Request Forms, (4) Policy on Gifts, Meals and Entertainment for Physicians and Other Healthcare Practitioners, (5) Policy on Promotional Meetings, (6) Policy on Preceptorships, (7) Policy on Funding to Support Independent Third-Party Educational or Scientific Meetings, (8) Policy on Grants or Support that Are not for Independent Medical Education, (9) Policy re: Sample Management, (10) Policy re: Employee Reporting of Adverse Events, Product Complaints, Tampering Adulteration and/or Diversion, (11) Policy on Providing Reimbursement Information to Customers. The 2004 Handbook emphasized compliance "with all applicable laws and regulations" and adherence "to good faith and professional standards in the conducts of its marketing and promotional activities."

In short, contrary to the State's allegations, the Teva and Actavis Generic Defendants did not engage in any unlawful acts in Oklahoma and, in fact, were committed to making sure they complied with applicable laws regarding marketing.

B. The Teva and Actavis Generic Defendants Cannot Be Held Liable For Statements Made By Third-Parties.

The State also attempts to hold the Teva and Actavis Generic Defendants liable for statements made by third-party organizations and key opinion leaders. But it cannot attribute to Defendants the statements made by others without establishing the existence of an agency relationship between the Defendants and the speaker. *See, e.g., Estate of King v. Wagoner County Bd. of County Com'rs*, 2006 OK CIV APP 118, ¶ 27 ("An agency relationship will not be presumed, and the burden of proving the existence, nature and extent of the relationship ordinarily rests on the party asserting it."). As a matter of law, evidence of funding alone is insufficient. *Murray County v. Homesales, Inc.*, 2014 OK 52, ¶ 15 ("The essential factor in any agency relationship is the principal's right to control the conduct of the agent.").

Here, each third-party organization that received funding from Cephalon, such as the American Pain Foundation, the Pain and Policy Studies Group, and the American Academy of Pain Management, has testified that it operated independently and was not influenced by anything the Teva or Actavis Generic Defendants said or did. Likewise, the content of third-party publications and CMEs was created independently from the Teva and Actavis Generic Defendants.

By way of example, the State's theory relies heavily upon a third-party publication, *Responsible Opioid Prescribing*, that was funded in part by Cephalon. But this publication was sponsored by many other agencies, non-profit corporations, and companies, including the American Cancer Society and the federal government. Critically, the author of this publication has confirmed that it was written to educate prescribers about the risks of opioids, and was created

entirely independent from any pharmaceutical influence. He controlled the content—and no one else. (Ex. K, S. Fishman, 2/26/19, 293:16–294:15.) In fact, prior to publication, *Responsible Opioid Prescribing* was subject to an advisory board committee that consisted of the future Surgeon General (Regina Benjamin) and many other well-respected medical professionals.

To make matters worse, *Responsible Opioid Prescribing* is neither false nor misleading as a whole. The first pages of the book warn about the risks and potential harm of opioid use—and the publication reiterates various tools prescribers should use before writing an opioid prescription, given their risks. (Ex. K, S. Fishman, 2/26/19 292:19–23.) Lastly, the State offers no evidence that any Oklahoma prescriber ever reviewed this publication—much less relied upon it to write a harmful opioid prescription.

In short, the State has not identified any nuisance committed by the Teva and Actavis Generic Defendants in the State of Oklahoma, and has chosen to ignore the many different sources of opioid-abuse problems in Oklahoma, such as illegal pill mills. Thus, judgment in favor of the Teva and Actavis Generic Defendants is appropriate.

VII. Any Allegedly False Marketing By The Teva Or Actavis Generic Defendants Did Not Impact The Community As A Whole, Much Less At The Same Time.

The State's entire public nuisance case against the Teva and Actavis Generic Defendants rests upon a handful of instances of marketing statements made by Cephalon out of millions of documents produced in this case. Such statements are not false and do not rise to the level of an unlawful act. But even if they did, there is no evidence that the alleged nuisance (*i.e.*, false marketing) impacted the entire Oklahoma community as a whole. 50 Okla. Stat. § 2 ("A public nuisance is one which affects ***at the same time*** an ***entire community*** . . .") (emphasis added).

Here, each Oklahoman did not receive marketing messages from the Teva or Actavis Generic Defendants, much less false marketing messages. Each Oklahoman did not receive a

prescription for an opioid medicine manufactured by the Teva or Actavis Generic Defendants; indeed, for those opioid medicines actually promoted by the Teva and Actavis Generic Defendants, very few prescriptions were actually written. The State certainly cannot show that any allegedly false marketing—as opposed to marketing generally or the conduct of others—was the cause of harmful opioid prescriptions for "an entire community" of Oklahomans. *Id.*

This principle is critical and cannot be cast aside. Oklahoma public nuisance law does not impose liability merely because the State can identify a few marketing statements by a manufacturer that the State (not Oklahoma prescribers) believes were misleading or that the State believes may have influenced a few prescribers. There is no public nuisance ***unless the public as a whole has been harmed by the nuisance***—here, the allegedly false marketing by the Teva and Actavis Generic Defendants. There is no evidence that a large number of Oklahoma prescribers received any false marketing by the Teva or Actavis Generic Defendants; that a large number of Oklahoma prescribers were supposedly deceived into writing opioid prescriptions by such marketing; or that a large number of patients were harmed by such prescriptions. Because there is no evidence that the Teva and Actavis Generic Defendants' false marketing caused harm to "an entire community" of Oklahomans "at the same time," 50 Okla. Stat. § 2, judgment in favor of the Teva and Actavis Generic Defendants is appropriate. *See City of McAlester v. Grand Union Tea Co.*, 1940 OK 39, 186 Okla. 487, 98 P.2d 924, 926 (acts of door-to-door salesman do not constitute nuisance because salesman "can only be at one place at one time and such a call cannot reasonably be said to disturb at the same time an entire community or neighborhood or any considerable number of persons.").

VIII. The State's Public Nuisance Claim Is Barred By Principles Of Equity, Including Unclean Hands, Laches, And Equitable Estoppel.

The State filed this lawsuit in 2017. But it knew of the dangers associated with opioid medicines well over a ***decade*** ago. The State also knew of the impact that opioid abuse had on individual Oklahomans for decades. The State could have taken measures to reduce the number of opioid prescriptions in Oklahoma and the harm it now complains about, but did not do so. As a matter of equity, the State cannot now hold the Teva or Actavis Generic Defendants responsible for such harm.

Under Oklahoma law, a party "who seeks equity must do equity and come into court with clean hands." *Story v. Hefner*, 540 P.2d 562 (Okla. 1975); *see also Krumme v. Moody*, 1995 OK 140, 910 P.2d 993, 996 (1995) (Oklahoma law declares that "to receive equity, [a person] must do equity."). Consistent with this basic principle of Oklahoma law, the State cannot obtain an equitable remedy if it contributed to the very harm for which it seeks relief. *See Walters v. Prairie Pil & Gas Co.*, 204 P. 906, 908 (Okla. 1922) (where plaintiffs and defendant oil company were both partially responsible for injury alleged, the court refused to hold defendants liable under nuisance theory). Nor can the State seek to take a legal position in this case inconsistent with its conduct over the time period at issue. *See, e.g., Oxley v. Gen. Atl. Res., Inc.,* 1997 OK 46, 936 P.2d 943, 947 ("Equitable estoppel holds a person to a representation made, or a position assumed, where otherwise inequitable consequences would result to another, who has in good faith, relied upon the representation or position.") And, of course, the State cannot pursue its equitable claim if it engaged in inexcusable delay in bringing this suit. *See, e.g., Smith v. Baptist Found. of Oklahoma*, 2002 OK 57, ¶ 8, 50 P.3d 1132, 1138 ("Laches is an equitable defense to stale claims.").

Contrary to the legal position it now takes, the State has affirmatively blessed the use of opioid medicines to treat long-term chronic pain by reimbursing for opioid prescriptions submitted

through the State Medicaid Program for precisely that condition (and others). And the State continues to do so today. The State could have imposed limitations to ensure that such prescriptions are limited to conditions the State believes are appropriate—yet it chose not to do so. Of course, the State's reimbursement practices influence what medicines are prescribed, dispensed, and consumed. The State cannot on the one hand argue that all opioid medicines prescribed for chronic pain are harmful and lead to addiction, yet, on the other hand, continue to permit (and condone) their use by reimbursing these very same prescriptions it deems harmful. Principles of equity preclude such conduct.

The State contributed to the alleged injury it now seeks billions of dollars to address in other ways, too. For example, the State could have passed legislation regulating when opioid prescriptions can be prescribed, and, if so, in what dosages and quantity limits. It did not. The State could have required prescribers and pharmacists to check the PMP prior to prescribing and filling opioid prescriptions at a much earlier date. It did not. The State could have passed pill mill legislation. It did not. The State could have provided more resources to address diversion and physician education. It did not. These are just a few examples. Because the State contributed to the very harm that it now argues was caused by the Teva and Actavis Generic Defendants, its remaining equitable claim for abatement must fail.

VIII. The State's Public Nuisance Claim Is Barred By The Two-Year Statute of Limitations.

The State's public nuisance claim is subject to a two-year statute of limitations unless (1) it is acting in its capacity as sovereign; and (2) a public right is implicated. *Oklahoma City Mun. Imp. Auth. v. HTB, Inc.*, 1988 OK 149, 769 P.2d 131, 137; *see Cole v. Asarco Inc.*, No. 03-CV-327-GKF-PJC, 2010 WL 711195, at *5 (N.D. Okla. Feb. 24, 2010) (imposing two-year statute of limitation period); *see also* 50 Okla. Stat. § 7 ("[n]o lapse of time can legalize a public nuisance,

amounting to an actual obstruction of ***public right.***") (emphasis added). Thus, if a public right is not involved, the two-year limitation period applies.

While the Oklahoma Supreme Court has not defined a public right in this context, other courts (and principles of common sense) make clear that "[a] public right is more than an aggregate of private rights by a large number of injured people. Rather a public right is the right to a public good, such as 'an indivisible resource shared by the public at large, like air, water, or public rights of way.'" *State v. Lead Indus., Ass'n, Inc.*, 951 A.2d 428, 448 (R.I. 2008) (internal citations omitted). Indeed,

> [u]nlike an interference with a public resource, "[t]he manufacture and distribution of products rarely, if ever, causes a violation of a public right as that term has been understood in the law of public nuisance. Products generally are purchased and used by individual consumers, and any harm they cause—even if the use of the product is widespread and the manufacturer's or distributor's conduct is unreasonable—is not an actionable violation of a public right. * * * The sheer number of violations does not transform the harm from individual injury to communal injury.

Id. (quoting Gifford, 71 U. Cin. L. Rev. at 817); *see also* Restatement (Second) of Torts § 821B (1979) (a public right is "collective in nature and not like the individual right that everyone has not to be assaulted or defamed or defrauded or negligently injured").

Here, there is no public right implicated. The alleged false marketing of prescription opioids to unidentified Oklahoma prescribers who treat specific patients in specific instances is not even close to analogous to the right of every member of the public to clean air or unpolluted public waterways. There is no public right for each resident of Oklahoma to be free of marketing to their physicians of opioid medicines. If the State seeks to regulate the conduct of pharmaceutical manufacturers, it can try to do so through the legislature. It has not done so. No matter how hard the State may try, it cannot turn a series of individualized opioid-related injuries into a public right to be free from commercial activity.

This principle is fatal to the State's claim. Because no public right is implicated, the State cannot bring a "public" nuisance claim—and, at a minimum, it was obligated to bring its public nuisance claim within two years after it allegedly was harmed by the nuisance. Indeed, the statute of limitations started to run as soon as the State "kn[e]w[] or, in the exercise of reasonable diligence, should have known of the injury." *Resolution Trust Corp. v. Grant,* 901 P.2d 807, 813 (Okla. 1995). The State has long argued that the opioid epidemic in Oklahoma started in 1996, with an increase in opioid-related overdoses occurring since that time. (Pet. ¶ 119). And Oklahoma agencies have long known of opioid-related injuries in Oklahoma. Yet the State waited until June 2017 to bring this lawsuit. Its remaining nuisance claim is therefore time-barred.

IX. The State's Abatement Remedy Is Inappropriate, Speculative, And Fatally Flawed.

The State has chosen to dismiss all remedies except one for abatement. Abatement is an equitable remedy akin to an injunction; it is separate and distinct from damages. *See, e.g., State v. Twin C Convenience Store*, 218 P.3d 529, 532 (Okla. Civ. App. Ct. 2009) (plaintiff sought to "obtain abatement of nuisances by injunction."). The statute also makes clear that the target of the abatement must be the "public nuisance." 50 Okla. Stat. § 11 ("A public nuisance may be abated by any public body or officer authorized thereto by law"). Thus, courts can provide "relief against either public or private nuisances by compelling the abatement, or restraining the continuance of the existing nuisance . . . ." *Magnolia Petroleum Co. v. Wright*, 124 Okla. 55, 254 P. 41, 45 (1926) (internal quotations and citations omitted)*; see also Simons v. Fahnestock,* 182 Okla. 460 (1938). Here, the State's abatement remedy is flawed for many reasons.

First, the alleged "nuisance"[7] is Defendants' purported false marketing. It is not, as the

[7] By seeking to abate the alleged nuisance, the State necessarily brings a claim for a temporary, as opposed to permanent, public nuisance. On April 11, 2019, the State conceded that it is asserting only a "temporary nuisance." (Ex. I, Apr. 11 Hr'g, 52–53); *see also Moneypenney v. Dawson*, 2006 OK 53, ¶ 9, 141 P.3d 549, 553 ("As a general proposition, '[w]hen a cause of an injury is abatable either by an expenditure of labor or money, it will not be held permanent.'" *Id.* (quoting *City of Ardmore v. Orr*, 1913 OK 50, 129 P. 867) (alteration in original)).

State would like the Court to believe, the damages that resulted from any alleged false marketing. *See Oklahoma City v. Page*, 1931 OK 764, 6 P.2d 1033, ¶ 10 ("A nuisance should be called 'nuisance' instead of 'damage.' 'Injury' is often used in a lay sense as meaning 'damage,' but in a legal sense it means 'wrong.' Injury is a wrong, and damage is the result. Nuisance is a wrong, and damage is the result."); *see also City of Holdenville v. Kiser,* 1945 OK 69, 195 Okla. 189, 156 P.2d 363, 364 ("As the terms are ordinarily used in nuisance cases, 'nuisance' is the wrong committed, 'damage' or 'injury' is the result of the nuisance, and 'damages' are the compensation for the damage or injury done."). Thus, to be a viable form of relief, the abatement remedy must be limited to curtailing the marketing and promotion of opioid medicines in Oklahoma. But the so-called "Abatement Plan" proposed by the State does no such thing. Instead, it seeks an award of billions of damages—not injunctive relief—to the Attorney General, and it seeks that money for various proposed measures to "abate the opioid crisis." Because the State's Abatement Plan is nothing more than a request for damages that the State already dismissed, judgment is appropriate.

Second, there is nothing to abate. The Teva and Actavis Generic Defendants no longer promote or market any opioid medicines in Oklahoma. Once again, abatement is the remedy to stop the alleged public nuisance (here, the alleged false marketing), *see* 50 Okla Stat. Ann. § 11 (stating "public nuisance may be abated")—not to pay damages on past consequences associated with the alleged nuisance. *See Atchison Topeka and S.F. v. Kelly*, 1928 OK 256, ¶ 10 ("The defendant might abate its nuisance, but that could not, by so doing, restore plaintiff's premises."); *Burlington Northern v. Grant*, 505 F.3d 1013, 1029 (10th Cir. 2007) (Oklahoma law) ("one aspect of damages the 'victim' of a temporary nuisance can recover 'is the cost of restoring the land to its former condition'" (quoting *Houck v. Hold Oil Corp.*, 1993 OK 166, 867 P.2d 451)). Because there is nothing to abate, there is no abatement remedy.

Third, the State's "Abatement Plan" has no legal basis. It is nothing more than a legislative budgetary wish-list dressed up as a purported judicial remedy. The State offers no way of practically overseeing the "Abatement Plan." It identifies no conduct that the Defendants must undertake. It identifies no basis for apportioning money in a way that meets legislative needs. Indeed, the level of judicial oversight that a decades-long "Abatement Plan" would impose not only an enormous burden on the Court, but also constitutional concerns of improper entanglement between the judiciary and legislature. *See, e.g., Fent v. Contingency Review Bd.*, 2007 OK 27, 163 P.3d 512, 517 (the legislative, executive, and judicial branches of Oklahoma government "shall be separate and distinct, and neither shall exercise the powers properly belonging to either of the others"); *Ex parte James*, 836 So. 2d 813, 819 (Ala. 2002) (holding court did not have authority to provide a specific remedy of directing the administration of funding for public schools, noting that "any specific remedy that the judiciary could impose would, in order to be effective, necessarily involve a usurpation of that power entrusted exclusively to the Legislature"). Not surprisingly, the State identifies no case that has ever approved the type of Abatement Plan that the State puts forward here. Nor can it.

Fourth, the State's "Abatement Plan" is entirely speculative and riddled with evidentiary and methodological flaws. As a threshold matter, the State offers no basis for the reasonableness, much less the necessity, of each component of its plan. No State witness can explain why each component of its plan is reasonable and supported by data and studies. In fact, the State's abatement plan improperly includes future costs that the State would have to bear ***even if the opioid crisis did not exist***, such as costs related to non-opioid pain treatment options and halfway houses. Similarly, many of the proposed projects address harms caused by other types of addiction, such as alcohol and methamphetamine addiction—which the State admits are major concerns unrelated

to opioid use. Worse yet, the "Abatement Plan" assumes that many of the costs for the proposed programs will remain steady or even increase over the next thirty years—which presumes that the very plan that the State proposes will be unsuccessful in the immediate future.

Lastly, the "Abatement Plan" seeks to provide money to the State for numerous expenses that it otherwise provides as a sovereign, such as emergency services and drug courts.[8] This is contrary to public policy and common law, which precludes recovery from a governmental entity for the "costs of carrying out public services from a tortfeasor whose conduct caused the need for the services." 32 A.L.R.6th 261 (originally published in 2008). The rationale for this rule is that state and local governments "provide core services for the public and pay for these services by spreading the costs to all citizens through taxation." *Baker v. Smith & Wesson Corp.*, No. CIV.A. 99C-09-283-FS, 2002 WL 31741522, at *5 (Del. Super. Ct. Nov. 27, 2002). The "Abatement Plan" ignores that legal principle (and many others).

X. Joint And Several Liability Does Not Apply As A Matter Of Law.

There is also no legal or factual basis to allow for joint and several liability. In 2009, Oklahoma sought to curb "lawsuit abuse" and did so, in part, by limiting the applicability of joint and several liability.[9] Joint and several liability is now nearly obsolete under Oklahoma law because the legislature deemed it contrary to public policy.

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[8] The Abatement Plan contains numerous other examples of services that the State already provides for which it seeks an award of money. Jessica Hawkins, who testified as an expert on the State's "Abatement Plan" and stated that many of the proposals are based off of programs already in place. (Ex. L, J. Hawkins Dep., 90:11–20; 185:20–22; 239:25–240:3.)

[9] The statute now precludes apportionment of joint and several liability, stating: "In any civil action based on fault and not arising out of contract, the liability for damages caused by two or more persons shall be several only and a joint tortfeasor shall be liable only for the amount of damages allocated to that tortfeasor." 23 Okla. Stat. § 15.

"Oklahoma's several liability statute now apportions liability by degree of fault rather than imposing joint liability." *Loos v. Saint-Gobain Abrasives, Inc.*, No. CIV-15-411-R, 2016 WL 5017335, at *6 (W.D. Okla. Sept. 19, 2016). The statute does make clear, however, that it "shall not apply to actions brought by or on behalf of the state." 23 Okla. Stat. § 15 (West). But the statute does not automatically apply joint and several liable in any action brought by the State—which would improperly ***expand*** the concept of joint and several liability (*i.e.*, the very thing the Oklahoma legislature sought to avoid). Instead, common law principles apply.

Under Oklahoma's common law, in order to be jointly and severally liable, the distinct acts of each defendant must "combine to produce directly a single injury." *Union Tex. Petroleum Corp. v. Jackson*, 909 P.2d 131, 149 (Okla. Ct. App. 1995). If the State's injury is not "single" but divisible, joint and several liability is not appropriate. *See, e.g., Atl. Ref. Co. v. Pack*, 180 P.2d 840, 843 (Okla. 1947); *Delaney v. Morris*, 145 P.2d 936, 939 (Okla. 1944); *White v. Taylor*, 728 P.2d 525, 526 (Okla. Ct. App. 1986). Here, there is no single injury. The State alleges a host of different individualized injuries to various consumers and to the State itself. (*See* Pet. ¶ 119 (*e.g.*, increase in non-medical use of painkillers, increase in number of heroin deaths, increase in healthcare, criminal justice, and lost work productivity expenses).) Even the State's so-called "Abatement Plan" seeks to address a number of different types of social harms and public expenses. And the State makes no effort to show that the different marketing (if any) by different manufacturers of different opioid medicines led to the same injuries.[10] While the State has repeatedly invoked the mantra of "joint and several liability," there is no evidence to trigger this

[10] It is implausible to suggest, and undisputed that the State cannot show, that the marketing of short-acting opioid medicines intended for breakthrough cancer pain led to any injuries, let alone combined to produce the same injuries as the marketing of broadly-indicated opioid medicines (such as OxyContin).

doctrine.

Oklahoma Supreme Court precedent makes clear that joint and several liability cannot apply here. In *Delaney v. Morris*, the Oklahoma Supreme Court held that the trial court erred by failing to instruct the jury that one defendant, Delaney, "could not be held liable for the injuries inflicted by [his co-defendant] Ark." 145 P.2d at 939. In that case, both defendants caused pollution that harmed the plaintiff's property. But their pollution entered the plaintiff's property through different ravines that were separate for a stretch before ultimately intersecting: "the two ravines carrying these polluted streams had no relation to each other until they joined." *Id.* at 938. As a result, there were "two separate and distinct sources of pollution which later, according to plaintiff's evidence, commingled and affected the land at a certain point but which prior thereto had left obvious and ascertainable separate and distinct effects upon other portions of the land." *Id.* Rejecting the trial court's instruction that the "jury was permitted to find a joint judgment against defendants," the Supreme Court held that there was "no rule of law that would have authorized Morris [plaintiff] to recover against Delaney [defendant] for the pollution cast onto Morris's land by Ark [defendant] where it was so clearly distinct and separable from that of Delaney." *Id* at 939; *see also Watson v. Batton*, 958 P.2d 812, 813 (Okla. Civ. App. 1998) (rejecting argument that drivers in two separate accidents were jointly responsible for plaintiffs' injuries because of the combined individsible effect of the two accidents).

Here, the State seeks to hold the Teva and Actavis Generic Defendants responsible for an array of different types of injuries associated with opioid usage—not a single injury. And, as in *Delaney* and *Watson*, these injuries purportedly stem from entirely separate marketing conduct by entirely separate Defendants (and third parties) at different times and to different audiences. The State, for instance, contends that Purdue created the opioid epidemic in 1996 through its marketing

of OxyContin. (Pet. ¶ 53.) But the Teva Defendants did not even start promoting any opioid medicines until many years later. Thus, they cannot be held jointly and severally liable for injuries stemming from Purdue's conduct in the marketing of OxyContin.

Notably, the State has done nothing to try to link any particular category of injury that requires abatement to any marketing conduct by the Teva or Actavis Generic Defendants. It has not surveyed Oklahoma prescribers to understand which Defendants' marketing, if any, they relied upon to write opioid prescriptions the State believes were harmful. It has not surveyed Oklahoma patients prescribed opioid prescriptions to understand whether patients benefited from these medicines and their pain was relieved. It has chosen not to analyze addiction and overdose data to understand which prescriptions it believes were prescribed improperly and then caused harm to Oklahomans. In fact, the State has refused to produce the information and data, in a usable format, that would be necessary to do such an analysis. This failure, of course, does not render any harm "indivisible." It merely means that the State cannot meet its causation burden—and certainly cannot proceed on a joint and several theory.

CONCLUSION

After nearly two years of litigation, the State has dropped all but one claim, and the lone remaining public nuisance claim has absolutely no legal or factual basis. The State cannot even offer a single Oklahoma doctor who will say that he or she was misled into writing a harmful opioid prescription because of some false marketing statement by the Teva or Actavis Generic Defendants—much less show that such marketing harmed an entire community of Oklahomans. The Teva and Actavis Generic Defendants do not even currently promote any opioid medicines, thereby negating any basis for the abatement relief sought by the State.

While Oklahoma faces a problem with opioid abuse and addiction, this is a situation that the Teva and Actavis Generic Defendants simply did not cause—and a problem for the Oklahoma legislature to address, not for the Court to try to remedy by acting as a super-legislature over a thirty-year period on issues over which the Court lacks expertise. Notwithstanding the State's rhetoric, this Court simply cannot ignore the myriad of legal and evidentiary flaws in the State's claim and hold the Teva and Actavis Generic Defendants responsible for what amounts to billions of damages to remedy harm caused by a multiple of independent actors (other than the Teva and Actavis Generic Defendants), including the State itself.

Dated May 23, 2019

Respectfully submitted,

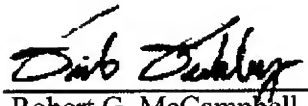

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EXHIBIT A

IN THE DISTRICT COURT OF CLEVELAND COUNTY
STATE OF OKLAHOMA

STATE OF OKLAHOMA, ex rel., MIKE HUNTER, ATTORNEY GENERAL OF OKLAHOMA,	§	
Plaintiff,	§	Case No. CJ-2017-816
vs.	§	The Honorable Thad Balkman
(1) PURDUE PHARMA L.P.; (2) PURDUE PHARMA, INC.; (3) THE PURDUE FREDERICK COMPANY; (4) TEVA PHARMACEUTICALS USA, INC.; (5) CEPHALON, INC.; (6) JOHNSON & JOHNSON; (7) JANSSEN PHARMACEUTICALS, INC.; (8) ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., n/k/a JANSSEN PHARMACEUTICALS, INC.; (9) JANSSEN PHARMACEUTICA, INC., n/k/a JANSSEN PHARMACEUTICALS, INC.; (10) ALLERGAN, PLC, f/k/a ACTAVIS PLC, f/k/a ACTAVIS, INC., f/k/a WATSON PHARMACEUTICALS, INC.; (11) WATSON LABORATORIES, INC.; (12) ACTAVIS LLC; and (13) ACTAVIS PHARMA, INC., f/k/a WATSON PHARMA, INC.,	§	William C. Hetherington Special Discovery Master
Defendants.	§	

NOTICE OF VOLUNTARY DISMISSAL OF CERTAIN CLAIMS WITHOUT PREJUDICE

Pursuant to Okla. Stat. tit. 12, §§ 683 and 684, the State of Oklahoma hereby voluntarily dismisses the following causes of action without prejudice to refiling: (1) violation of the Oklahoma Medicaid False Claims Act, (2) violation of the Oklahoma Medicaid Program Integrity Act, (3) Fraud (Actual and Constructive) and Deceit, (4) Unjust Enrichment, and (5) compensatory damages, including past damages stemming from its public nuisance claim. The State does not

dismiss, and will continue to pursue, its cause of action for public nuisance and remedy of abatement under Okla. Stat. tit. 50, §§ 1–2, 8, 11, as well as any and all further equitable relief deemed just and proper.

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EXHIBIT B

IN THE DISTRICT COURT OF CLEVELAND COUNTY

STATE OF OKLAHOMA

STATE OF OKLAHOMA, ex rel., MIKE HUNTER ATTORNEY GENERAL OF OKLAHOMA, Plaintiff, vs. (1) PURDUE PHARMA L.P.; (2) PURDUE PHARMA, INC.; (3) THE PURDUE FREDERICK COMPANY; (4) TEVA PHARMACEUTICALS USA, INC; (5) CEPHALON, INC.; (6) JOHNSON & JOHNSON; (7) JANSSEN PHARMACEUTICALS, INC.; (8) ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., n/k/a JANSSEN PHARMACEUTICALS; (9) JANSSEN PHARMACEUTICA, INC. n/k/a JANSSEN PHARMACEUTICALS, INC.; (10) ALLERGAN, PLC, f/k/a ACTAVIS PLC, f/k/a ACTAVIS, INC., f/k/a WATSON PHARMACEUTICALS, INC.; (11) WATSON LABORATORIES, INC.; (12) ACTAVIS LLC; AND (13) ACTAVIS PHARMA, INC., f/k/a WATSON PHARMA, INC., Defendants.	Case No. CJ-2017-816

TRANSCRIPT OF PROCEEDINGS
HAD ON AUGUST 30, 2018
AT THE CLEVELAND COUNTY COURTHOUSE
BEFORE THE HONORABLE THAD BALKMAN
DISTRICT JUDGE

REPORTED BY: ANGELA THAGARD, CSR, RPR

made -- we have not presented any illusions about the fact that we intend to use statistical modeling to present that claim. That is something that is done in false claims cases.

We'll at some point present that issue to Judge Hetherington when we talk about what the discovery scope should look like with respect to our responses. It's not uncommon at all in false claims cases. It's not uncommon here.

Mr. Burrage and Mr. Whitten successfully tried the Burgess case where statistical sampling was used there on a bad faith fraud claim that was affirmed by the Supreme Court. It's not an unheard of issue. In fact, it's quite common.

Our nuisance claim is different, though, your Honor. The nuisance claim doesn't require intent. It doesn't require reliance. It doesn't require proof of fraud. It requires unlawful conduct.

And as we talk about how this case gets presented, going back to the history a little bit, we had an opioid crisis and epidemic in this country around 1870 to 1900; people coming back from the civil war with a lot of problems. And we had doctors and others that were giving away heroin and opioid-based products. It was really bad. It was a national epidemic.

Through education and outreach, the government was able to stop that problem. In 1915 there was a law that was passed that dealt with the controlled substances, and then we had

prohibition that came after it. But a lot of what happened with those laws was unnecessary by that time because we had educated the public and doctors about the dangers associated with opioid addiction and abuse and misuse.

One of the things that had to happen was not only that we educated doctors, but that folks that had been prescribing and giving away those types of drugs had to get out of the system, and we had to have different, better educated, and differently educated folks come into the system and understand that this was not the way to treat pain in this country.

From 1915 to 1996, we didn't have this problem. The opioid epidemic had been discovered and it had been caged and it was not a problem. Yes, we had some heroin. Yes, we had some Oxycodone related issues; percodan -- or percocet created some problems. But we didn't have a widespread opioid epidemic. We didn't.

1996, Purdue let the lion out of the cage, and it has run wild and it has destroyed parts of this country state by state. And you can watch it move across the map on a timeline and see how it got here. But that's what happened.

You can trace it to a very specific point in time, and that is when OxyContin was brought to market and promoted in an aggressive, concentrated, and targeted way to consumers and doctors, practitioners, prescribers, and pharmacists across this country. That's what happened. That's what we're dealing

with.

And so this case on the nuisance claim will be very simple. Is there a crisis; does it affect the public health. Does it affect the public at large, and did the defendants commit some unlawful act that got us there.

But that unlawful act doesn't have to be intent and it doesn't have to be fraud and it doesn't require reliance and it doesn't require clear and convincing evidence. And it really is that simple. I'm not saying the case is simple. It's not. It is complex and it is hard.

And I'll just leave you with this. We've heard a lot about Tobacco because it was a very important case. As Mr. Brody talked about, I think he worked at the Department of Justice during part of their Tobacco endeavors. It's been an important part of my life and our firm.

But hearing somebody that wasn't involved in that case talk about what actually happened there is kind of like yogi bear used to say, it's deja vu all over again. Judge Folsom trifurcated that case.

If you look at that order, what he said about Rule 42(B) is it provides a very important mechanism that is desperately needed in this day of complex litigation. That was in 1997. That was one year after Purdue let the lion out of the cage. There is a lot that has happened since then.

And there are courts, state courts and federal courts

across this country, who have relied upon whatever their version of what this rule is to bifurcate trials, whether by claim or by issue.

I would submit to the Court that this can be done. I would submit to the Court that it should be done. And I would submit to the Court that one of the great powers you'll have, if you choose to use one jury for this, is that -- we talk about efficiency and economy and witnesses, you know. You have the power to control us as lawyers and the parties on how we present our claims and facts to a jury.

And if we get to the second phase and issues have been decided or facts that you've already seen, your Honor, presented to the jury, and you understand them better, the same jury is sitting there and they've already heard it, I think you will be able to narrow quite heavily how and what is presented to the jury as we go forward with those other issues.

So I don't mean to say it's simple in the sense that it's not important, and this is a heavy issue. It is. But I think putting this nuisance claim out on its own in the phase 1 is the right way to go. Thank you, your Honor.

THE COURT: Thank you, Mr. Beckworth.

Go ahead.

MR. BRODY: Can I just make one point in response, and it's a very simple point, your Honor. The mere fact that elements may vary from count to count makes no difference for

EXHIBIT C

Initial REMS approval: 12/2011

Most recent modification: 12/2014

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **outpatient** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for <u>all</u> patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access <u>*Patient-Prescriber Agreement Form*</u> with <u>each</u> new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.

2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

3) I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

4) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

5) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

6) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

7) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in

the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.

3) I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock, for my constant pain, then I must also stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access

Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

   i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

   ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

   - *TIRF REMS Access Prescriber Program Overview*
   - *TIRF REMS Access Education Program*
   - *Knowledge Assessment*
   - *Prescriber Enrollment Form*
   - *Patient-Prescriber Agreement Form*
   - *TIRF REMS Access Patient and Caregiver Overview*
   - *Frequently Asked Questions (FAQs)*
   - *TIRF REMS Access Website*

   iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

   iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

   v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

   vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they

must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* is part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain and closed system outpatient pharmacies) or authorized pharmacist (independent outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. For the purposes of this REMS, there are different requirements for :

- **Outpatient Pharmacies**

  i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chain stores) in the TIRF REMS Access program.

  ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

  iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.

- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

d. ***Chain and Independent Outpatient Pharmacy(s):***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **chain or independent outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment.*

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Independent Outpatient Pharmacy Enrollment Form* or the *Chain Outpatient Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

o) I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Note: The *'or the designated chain pharmacy cash bin'* language will not be included in the attestation on the Independent Outpatient Pharmacy Enrollment Form

e. ***Closed System Outpatient Pharmacies*:**

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment.*

ii. Complete and sign the *Closed System Outpatient Pharmacy Enrollment Form.* In signing the *Closed System Outpatient Pharmacy Enrollment Form*, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located

on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.*

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear*

Pharmacy Letters will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. **TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.**

   a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

   b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.

   c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

      i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

      ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

   d. For **closed system outpatient pharmacies:** prior to dispensing TIRF medicines, enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

      i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

      ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

   e. Following initial activation, patient PPAFs remain active until a trigger for inactivation occurs. Triggers for PPAF inactivation include:

      i. The patient has not filled a prescription for more than six (6) months.

ii. The PPAF has expired.

iii. The patient is deceased.

iv. The patient chooses to no longer participate in the TIRF REMS Access program.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

2. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

      i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

      ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

      iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

      iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

   c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

   d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

4. For **chain and independent outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

5. For **closed system outpatient pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system for **chain and independent outpatient pharmacies** or through the call center for **closed system outpatient pharmacies**.

7. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system outpatient pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

8. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
9. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
10. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
11. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
12. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
13. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Prescribers

To prescribe TIRF medicines for outpatient use, Prescribers must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

NOTE: There are different requirements for inpatient prescribers that only prescribe TIRF medicines for inpatient use. For inpatient administration (e.g. hospitals, in-hospital hospices, and long-term care facilities that prescribe for inpatient use), of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Only the inpatient pharmacy and distributors are required to be enrolled to be able to order and dispense TIRF medicines for inpatient use. Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Overview of the TIRF REMS Access Program for Prescribing to Outpatients: Steps for Enrollment and Program Requirements

Prescriber Education & Enrollment (Outpatient Use)

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS program do I need to enroll in the shared TIRF REMS Access Program?

All prescriber enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following three sections provide detailed information on the Enrollment Process (Section 1), the Patient Program Requirements (Section 2), and the Prescribing Process (Section 3) for outpatient prescribing of TIRF medicines.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Create an account and complete registration at www.TIRFREMSaccess.com.
2. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
3. Complete and submit a Prescriber Enrollment form.

Detailed Enrollment Process

Step 1: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account and complete registration at www.TIRFREMSaccess.com.

  How do I create an account and complete the TIRF REMS Access registration on-line?
  - Select the 'Create My Account' button on the home page
  - Complete the Create Account Information section
  - Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' question
  - Create User ID and Password and select 'Create My Account'
  - Select 'Prescriber' as the option to best describe you and select 'Continue'

- Complete required fields on the Prescriber Registration page and select 'Submit' to continue
- Complete required fields in the 'Site Information' section by adding your site and select 'Submit'

Step 2: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully
- Select 'Complete Enrollment' to continue

Step 3: Complete and submit Prescriber Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Prescriber Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to review the demographic information previously submitted, read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Patient Program Requirements

Summary of Patient Program Requirements

1. Identify appropriate patients
2. Counsel patients
3. Complete and submit the TIRF REMS Access Program Patient-Prescriber Agreement Form

Detailed Patient Program Requirements Process

Step 1: Identify appropriate patients

- Identify appropriate patients based on the guidance provided in the TIRF REMS Access Education Program and the product-specific Full Prescribing Information. Full Prescribing Information is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 2: Counsel Patients

- Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide. A Patient and Caregiver Overview is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 3: Complete and submit the TIRF REMS Access Patient-Prescriber Agreement Form

- Complete the TIRF REMS Access Program Patient-Prescriber Agreement Form, for each new patient, which must be signed by both you and your patient (not required for inpatients).

NOTE: A prescriber must be enrolled in the TIRF REMS Access program to submit a Patient-Prescriber Agreement Form for a patient.

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form by fax?

- Obtain a TIRF REMS Access Patient-Prescriber Agreement Form. A printable version of the Patient-Prescriber Agreement Form is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Review the TIRF REMS Access Patient-Prescriber Agreement Form with your patient.
- Complete Prescriber required fields.
- Have the patient or caregiver complete the patient required fields.
- Submit Patient-Prescriber Agreement Form by fax to **1-866-822-1487.**

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form online?

- Log in to the TIRF REMS Access program from the home page by entering in your User ID and Password
- Select the heading labeled 'My Account'
- Select the 'PPAF' link
- Review the TIRF REMS Access Patient-Prescriber Agreement Form
- Enter your electronic signature, today's date, and check the attestation box
- Enter the required patient information
- Have the patient enter their electronic signature, today's date, and check the attestation box
    - (NOTE: If applicable, a Patient Representative can enter in their information in the required section on behalf of the patient)
- Print off two copies of the form by selecting the 'Print' button
- Provide one copy to the patient and keep one for your records
- Select the 'Submit' button to submit the PPAF for the patient
- You can print the confirmation by selecting the 'Print Confirmation' button

Section 3: Summary of Prescribing Process

1. Write TIRF medicine prescription.
2. Help patient find an enrolled pharmacy.

Detailed Prescribing Process

Step 1: Write TIRF medicine prescription

- Write a prescription for the appropriate TIRF medicine.

Step 2: Help patient find an enrolled pharmacy

- Help each patient find pharmacies which are enrolled in the TIRF REMS Access program. A list of enrolled pharmacies can be found on www.TIRFREMSaccess.com, or by calling **1-866-822-1483**.
- Inform patients that they can also find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or

- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Transmucosal Immediate Release Fentanyl (TIRF) Products Risk Evaluation and Mitigation Strategy (REMS)

TIRF REMS Access Program

Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl buccal tablet)
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

TIRF REMS Access Education Program:

- Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.
- The Education Program and enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.
- Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.
- Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

- This Education Program contains key safety information critical for minimizing the risks associated with TIRF medicines.
- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up

TIRF REMS Access Education Program

Overview (cont.)

- Information on the TIRF REMS Access program requirements and operations is provided in the TIRF REMS Access program overviews for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com.
- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.
- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guide for each product prescribed.

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patients with cancer 18 years of age and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain.**
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.
- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids.

Appropriate Patient Selection (cont.)

Definition of Opioid Tolerance:

- Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - OR an equianalgesic dose of another oral opioid
- TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Appropriate Patient Selection (cont.)

Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients.
- TIRF medicines are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain. Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.
- TIRF medicines are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some fentanyl products.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction and Overdose

- TIRF medicines contain fentanyl, an opioid agonist and Schedule II controlled substance. TIRF medicines can be abused in a manner similar to other opioid agonists, legal and illicit.
- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.
- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse
- Concerns about abuse and addiction should not prevent the proper management of pain.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, and Addiction and Overdose (cont.)

- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.
- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines
- Manage the handling of TIRF medicines to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting, and as required by law.

Determine Patient-Specific Risk Factors

2. Accidental Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- TIRF medicines must be stored safely and kept out of reach of children of all ages ***at all times***, including toddlers through teens.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.
- Any accidental exposure can be fatal. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may result in potentially dangerous increases in fentanyl plasma concentrations, which could increase or prolong the drug effects and may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.

Dosage and Administration General

- **Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine.** Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are **not equivalent** to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.

Dosage and Administration General

Appropriate Conversion

- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine **must not be done on a microgram-per-microgram basis** and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
    - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora, Actiq to Subsys, and Actiq to Abstral, you must refer to the Full Prescribing Information for detailed instructions.

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a successful dose is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the breakthrough cancer pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

Products** Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Abstral is always 100 mcg (unless the patient is being converted from ≥400 mcg ACTIQ - please see Full Prescribing Information).	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100mgc dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl buccal tablet)	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per cancer breakthrough pain episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough pain episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl buccal soluble film)	Always 200 mcg	**ONSOLIS should be used only once per breakthrough cancer pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.
Subsys® (fentanyl sublingual spray)	SUBSYS is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ – please see Full Prescribing Information.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of SUBSYS per episode of breakthrough pain.	Patients must wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.	Closely follow patients and change the dosage level until adequate analgesia is achieved using a single dose per episode of breakthrough cancer pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**

- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.
- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.
    - **Note: Patients have had difficulty comprehending this concept; please emphasize it to your patients.**

Patient Counseling

Tell the patient (cont.):

- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You much take TIRF medicines exactly as prescribed.
- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*

Patient Counseling

Tell the patient (cont.):

- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

➢ **All patients treated with opioids require careful monitoring. At follow-up visits:**

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of their around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
    - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
    - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.